Ezetimibe (Zetia®) Criteria for Nonformulary Use

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

September 2005

The following recommendations are based on current medical evidence. The content of the document is dynamic and will be revised as new clinical data become available. The purpose of this document is to assist practitioners in clinical decision making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician, however, must make the ultimate judgment regarding the propriety of any course of treatment in light of individual patient situations.

Ezetimibe (Zetia®) is the first in a new class of cholesterol lowering agents called the cholesterol absorption inhibitors. It acts by selectively inhibiting absorption of cholesterol (dietary and biliary) at the brush border of the small intestine. In addition to other rare, more severe forms of hypercholesterolemia, ezetimibe is FDA approved in combination with statins or alone for the management of primary hypercholesterolemia.

Most of the large statin trials, demonstrating a reduction in adverse cardiovascular health outcomes, utilized moderate to higher statin doses versus placebo (e.g. 4S-simvastatin 20-40 mg/d, HPS-simvastatin 40 mg/d). In addition, incremental effect has been observed with high dose statin versus lower dose statin (TNT-atorvastatin 10 vs 80 mg).[1] It is not known whether the same clinical effect will be seen if a low dose statin is combined with ezetimibe or another agent (bile acid sequestrant or niacin). Additionally, there is emerging evidence to suggest that there may be differing effects of high versus lower dose statins or ezetimibe in measures of endothelial function (pleiotropic effects).

At this time, there is no evidence with ezetimibe monotherapy or when combined with a statin to support a reduction in cardiovascular health outcomes (nonfatal myocardial infarction, coronary heart disease death, etc). However, there is currently one clinical outcomes trial (IMPROVE-IT) and one atherosclerotic progression trial (ENHANCE)[2] that are underway to determine the incremental effect of adding ezetimibe to statins.

For patients not achieving their LDL-C goals with moderate to high-dose statins (or the highest recommended or tolerated statin dose), clinicians may choose to maximize the statin dose or consider addition of a second lipid-lowering agent. If the LDL-C is within 10% of goal, the preferred step is to maximize statin therapy. However, if the LDL-C is more than 10% above goal, combination therapy may be considered. If combination therapy is selected, clinicians are advised to consider add-on therapy with niacin prior to combination therapy with ezetimibe (because of ezetimibe's lack clinical outcome data). In HATS (HATS-Brown 2001), the combination of statins plus niacin led to net regression of atherosclerosis and a relative reduction in clinical events of 90% compared to placebo.[3] However, in the ARBITER 2 trial, the addition of niacin to simvastatin did not improve atherosclerotic progression versus simvastatin alone.[4] In a third study by Hecht, et al,[5] patients with evidence of subclinical atherosclerosis received a combination of statins plus niacin or statins alone. In this particular study, the patient's treating physician chose the lipid-lowering agent and dose based upon clinical considerations that were not dictated by the study. As a result, significantly more patients on combination therapy had lower baseline HDL and higher baseline triglycerides (TG) than those receiving statin monotherapy. Calcified plaque progression was similar between the statin monotherapy group (who had normal HDL-C and TG) and the group receiving the statin-niacin combination (with elevated TG and low HDL-C). As a result, the authors concluded that similar benefit was seen between statins alone and the niacin-statin combination despite the less desirable lipid levels in the combination group at baseline.

There are some patients that may not be candidates for niacin including those with a history of confirmed peptic ulcer disease (perforation, ulceration or upper gastrointestinal bleeding), gouty attacks (as evidenced by the presence of intra-articular uric acid crystals in the affected joint) and/or poorly controlled diabetes. However, two recent trials demonstrated the safety and efficacy of an extended release niacin product (Niaspan 1000-3000mg/d) in diabetics managed by diet, oral hypoglycemics, or insulin.[6-7] Although hemoglobin A1C was statistically increased at higher niacin doses in one study, the changes may not be considered clinically significant (Baseline and end of study hemoglobin A1C changed from 7.2% to 7.5% in the niacin 1500 mg group-p=0.048).[6] There were no significant changes in hemoglobin A1C in the niacin 1000 mg group. In the second study, there were no significant changes in hemoglobin A1C in patients using up to 3 grams daily of niacin.[7] In those patients not reaching their LDL-C goals with add-on niacin; unable to tolerate niacin; or are not candidates for niacin, addition of either a bile acid sequestrant (BAS) or ezetimibe (nonformulary) can be considered. (*See appendix A, page 4 for considerations with niacin therapy).

Ezetimibe should not be considered first line for patients with elevated LDL-C who cannot tolerate statins since there are other lipid-lowering therapies (niacin or BAS) with clinical trial evidence to support reductions in coronary heart disease (CHD) outcomes. However, ezetimibe may be considered as monotherapy in patients unable to tolerate statins and having an inadequate LDL-C lowering response, intolerance or contraindication to therapeutic doses of niacin and BAS.

More detailed information regarding ezetimibe and references used can be obtained from the ezetimibe monograph located on the following websites: www.pbm.va.gov or http://vaww.pbm.va.gov. Updated versions may be found on the same websites.

1. Potential Candidates For Ezetimibe (Patients who have met their LDL-C goal on statin monotherapy should NOT be switched to combination therapy with ezetimibe)

A. In Combination with Statins:

_____ LDL-C goal not achieved with moderate[1] to high-dose statin or maximally tolerated or recommended dose of statin (drug-drug interaction, etc.) [Guidance: If LDL-C is within 10% of goal, preferred step is to maximize statin dose. If LDL-C is more than 10% above goal, combination therapy can be considered.]

AND

_____ LDL-C goal not achieved with niacin, unable to tolerate niacin or may not be a candidate for niacin (e.g. history of confirmed peptic ulcer disease [perforation, ulceration or upper GI bleeding] gouty attacks [as evidenced by the presence of intra-articular uric acid crystals in the affected joint] and/or poorly controlled diabetes).

B. Monotherapy:

_____ Unable to tolerate statins[5]

AND

_____ Inadequate LDL-C lowering response, intolerance or contraindication to therapeutic doses of niacin and bile acid sequestrants.[4]

[1]Moderate to high-dose statins: atorvastatin (nonformulary) 40-80 mg, fluvastatin 80 mg, lovastatin 80 mg, pravastatin 80 mg (nonformulary), rosuvastatin (nonformulary) 20 mg or simvastatin 40-80 mg.
[2]Product labeling for ezetimibe recommends against combining ezetimibe with fibrates until human studies have been completed.
[3]If BAS are combined with ezetimibe, ezetimibe should be taken 1-2 hours before or 4-6 hours after the BAS.
[4]Monotherapy with BAS is contraindicated in patients with triglyceride levels >400 mg/dL and in familial dysbetalipoproteinemia. Avoid in patients with triglyceride levels >400 mg/dL
[5]There is emerging evidence suggesting patients with common features of impaired fatty acid oxidation may have recurrence of their myopathic symptoms on ezetimibe as well as niacin, fibrates and statins.
[6]For other possible LDL-C lowering strategies and considerations, refer to appendix A, pages 4&5.

2. Criterion For Discontinuing Ezetimibe

Due to the potential variability in response to cholesterol absorption inhibitors, and since the maximum LDL-C response from ezetimibe can be seen as early as 2 weeks, assessment of response should be made within the first 4-6 weeks of therapy. If a patient does not experience a substantive response, usually a decrease in LDL-C by 10 to 15% toward goal, ezetimibe should be discontinued.

3. Safety Considerations

a. Ezetimibe is not recommended in patients with moderate or severe liver impairment because the effects of increased exposure to ezetimibe are not known.
b. Clinically significant elevation (>3 times upper limit of normal) in liver function tests were seen in a significantly greater number of patients receiving ezetimibe plus a statin (1.3%-2%) versus a statin alone (0.4%). When ezetimibe is used in combination with statins, LFTs must be monitored (see section 5 below).
c. Several cases of myopathy have been reported in patients receiving high-dose statins upon initiation of ezetimibe. As a result, caution should be used when adding ezetimibe to statins, especially in patients more susceptible to statin myopathy (e.g. advanced age, frailty, female gender, drug-drug interactions, hypothyroidism, alcoholism, etc.)[10-11]
d. Generally, ezetimibe should not be combined with fibrates until human studies are completed (potential for increased risk of cholelithiasis in combination).
e. Triple therapy with statins, BAS or niacin, and ezetimibe is generally not recommended since efficacy and long-term safety are uncertain.
f. The combination of ezetimibe with BAS or niacin is generally not recommended since there are no published data demonstrating safety and efficacy of the combination, unless no other alternatives exist. In addition, the LDL-C lowering effect of ezetimibe may be reduced in the presence of BAS.
g. All patients receiving statins, including those receiving combination therapy with ezetimibe, should be informed regarding the recognition and reporting of any unexplained muscle pain, tenderness or weakness.

h. For additional data on safety, including drug-drug interactions, see the ezetimibe monograph at http://www.pbm.va.gov or http://vaww.pbm.va.gov

4. Dosage and Administration

The manufacturer's recommended dose is 10 mg daily without regard to meals. However, some advocate using a 5 mg dose. In a pooled analysis of two-phase II studies, the LDL-C lowering response of 0.25 mg, 1 mg, 5 mg and 10 mg of ezetimibe (monotherapy) was examined in 432 patients for 12 weeks. The 5 mg dose reduced LDL-C by 15.7% and the 10 mg by 18.5% ($P<0.05$ in favor of 10 mg dose). In the 5 mg group, 54% of patients had a reduction in their LDL-C of $\geq$15% and 67.8% of those in the 10 mg group had reductions in their LDL-C of $\geq$15%.[8] In another study, a small number of patients (n=8 in each group) were randomized to lovastatin 20 mg, lovastatin 20 mg + ezetimibe 5 mg, lovastatin 20 mg + ezetimibe 10 mg, lovastatin 20 mg + ezetimibe 20 mg or lovastatin 40 mg + ezetimibe 10 mg for 2 weeks. Addition of ezetimibe resulted in an additional reduction in LDL-C of 16-18% compared to lovastatin alone. There were no differences in LDL-C lowering response observed between 5, 10 or 20 mg of ezetimibe.[9]

5. Monitoring

When ezetimibe is administered in combination with a statin, LFTs should be performed prior to initiation of therapy and according to the recommendations of the statin (e.g. simvastatin: within the first 12 weeks, and periodically thereafter).

6. References

1. LaRosa JC, Grundy SM, Waters MD, et al. Intensive Lipid Lowering With Atorvastatin in Patients with Stable Coronary Artery Disease. NEJM 2005;352: (published online 3-05) http://content.nejm.org/cgi/reprint/NEJMoa050461v1.pdf
2. Kastelein JP, Sager PT, deGroot E, Veltri E. Comparison of Ezetimibe Plus Simvastatin Versus Simvastatin Monotherapy on Atherosclerosis Progression in Familial Hypercholesterolemia: Design and Rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) Trial. Am Heart J 2005;149:234-239
3. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and Niacin, Antioxidant Vitamins, or The Combination For The Prevention of Coronary Disease. N Engl J Med 2001;345:1583-1592.
4. Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2. A Double-Blind, Placebo-Controlled Study of Extended-Release Niacin on Atherosclerosis Progression in Secondary Prevention Patients Treated with Statins. Circulation 2004;110:3512-3517.
5. Hecht HS, Harman SM. Comparison of Effectiveness of Statin Monotherapy Versus Statin and Niacin Combination Therapy in Primary Prevention and Effects on Calcified Plaque Burden. Am J Cardiol 2003;91:348-351.
6. Grundy SM, Vega GL, McGovern ME, et al. Efficacy and Safety, and Tolerability of Once-Daily Niacin for the Treatment of Dyslipidemia Associated with Type 2 Diabetes. Arch Intern Med 2002;162:1568-1576.
7. Elam MB, Hunninghake DB, Davis KB, et al. Effect of Niacin on Lipid and Lipoprotein Levels and Glycemic Control in Patients with Diabetes and Peripheral Artery Disease. The ADMIT study: A Randomized Trial. JAMA 2000;284:1263-1270.
8. Bays HE, Moore PB, Drehobl MA, et al. Effectiveness and Tolerability of Ezetimibe in Patients with Primary Hypercholesterolemia: Pooled Analysis of Two Phase II Studies. Clin Ther 2001;23:1209-1230.
9. Kosoglou T, Statkevich P, Meyer I, et al. Effects of Ezetimibe on the Pharmacodynamics and Pharmacokinetics of Lovastatin. Curr Med Res and Opin 2004;20:955-965.
10. Fux, et al. Ezetimibe and Statin-Associated Myopathy. Ann Intern Med 2004;140:671-672.
11. Phillips PS. Ezetimibe and Statin-Associated Myopathy Ann Intern Med 2004;141:649.

More detailed information regarding ezetimibe and references used can be obtained from the ezetimibe monograph located on the following websites: http://www.pbm.va.gov or http://vaww.pbm.va.gov. Updated versions may be found on the same websites.

Appendix A: Possible LDL-C Lowering Strategies For Patients Not Achieving Their LDL-C Goals with Moderate to High-Dose Simvastatin or High-Dose Atorvastatin (In general, data are unavailable to support advantages in clinical outcomes when comparing one LDL-C lowering strategy to another).

Scenario #1: Patient on Simvastatin 40 mg and has not met LDL-C Goal:

LDL-C Lowering Strategy	Estimated Mean % LDL-C Reduction (approximate)	Additional Cost $/Month	Total Cost $/Month
Increase simvastatin to 80 mg	6-7%	7.20	28.20
Addition of cholestyramine 4-8 grams/day	15%	11.64-23.28	32.64-44.28
Addition of up to niacin 2 grams [b]/day	15%	25.20 (Niaspan)	46.20
Switch to simva 40/ ezetimibe 10 (Vytorin)+	15%	28.50	49.50
Addition of ezetimibe 10 mg	15%	42.90	63.90
Addition of colestipol 15 gm/day (packets)	15%	87.70	108.70

Scenario #2: Patient on Simvastatin 80 mg and has not met LDL-C Goal:

LDL-C Lowering Strategy	Estimated Mean % LDL-C Reduction (approximate)	Additional Cost $/Month	Total Cost $/Month
Addition of cholestyramine 4-8 grams/day	15%	11.64-23.28	32.64-44.28
Switch to simva 80/ ezetimibe 10 (Vytorin)+	15%	24.30	52.50
Addition of up to niacin 2 grams [b]/day	15%	25.20 (Niaspan)	53.40
Switch to atorvastatin 80 mg	5-6%	33.60	61.80
Addition of ezetimibe 10 mg	15%	42.90	71.10
Addition of colestipol 15 gm/day (packets)	15%	87.70	115.90

Scenario #3: Patient on Atorvastatin 80 mg and has not met LDL-C Goal:

LDL-C Lowering Strategy	Estimated Mean % LDL-C Reduction (approximate)	Additional Cost $/Month	Total Cost $/Month
Switch to simva 80/ ezetimibe 10 (Vytorin)	6-7%	-9.30	52.50
Switch back to simvastatin 40 to 80 mg with ezetimibe 10 mg (if tried niacin first) [a]	6-7%	2.10 to 9.30	63.90 to 71.10
Addition of cholestyramine 4-8 grams/day	15%	11.64-23.28	73.44-85.08
Addition of niacin up to 2 grams [b]/day	15%	25.20 (Niaspan)	87.00
Addition of ezetimibe 10 mg	15%	42.90	104.70
Addition of colestipol 15 gm/day (packets)	15%	87.70	149.50

[a] In two clinical trials, the difference in LDL-C lowering between simvastatin 40/ezetimibe 10 and simvastatin 80/ezetimibe 10 was only 1.2-3.8% in favor of the higher dose. (Ballanytne, et al Am Heart J 2005;149:464-473, Ballantyne, et al. Am J Cardiol 2004;93:1487-1494)

[b] To reduce flushing, niacin must be titrated. (See bottom of page 6 for example titration schedules).

Prices do not take into account tablet splitting

CONSIDERATIONS FOR POSSIBLE LDL-C LOWERING STRATEGIES

LDL-C Lowering Strategy	Considerations
Increasing statin dose	• As the dose of statins increase, so does the risk for LFT elevation and myopathy
Addition of niacin	• Combination of niacin and statins may increase risk for myopathy. • Most common adverse event of niacin is flushing. To limit niacin-associated flushing, niacin must be titrated (see below for titration schedules). Prior to initiation of niacin, discussion of the potential for flushing with patient and strategies for reducing occurrence and severity of flushing is recommended. (e.g. Improves with continued administration, can be improved by taking ASA or other nonsteroidal anti-inflammatory agent (e.g. ibuprofen) 30 minutes prior to niacin and avoiding alcohol, spicy foods and hot drinks around the time of niacin administration.) • Avoid in patients with a history of confirmed perforation, ulcer or GI bleeding. • Avoid in patients with a history of confirmed gout (as evidenced by intra-articular uric acid crystals in the affected joint). • Use with caution in diabetics, may alter glycemic control • Can reduce LDL-C 15-20%, TG by 20-35% and increase HDL-C by 15-30%
Addition of ezetimibe	• The combination of ezetimibe plus statins has resulted in a greater incidence of clinically significant (>3x ULN) elevation in LFTs vs. statins alone. LFTs should be monitored • There are some reports of myopathy after adding ezetimibe to high dose statins, use caution in those patients more susceptible to myopathy (e.g. older age, frailty, alcohol abuse, renal or liver impairment, hypothyroidism)
Addition of bile acid sequestrant (BAS)	• May increase triglyceride concentrations. Avoid in patients with TG levels in excess of 400 mg/dL and those with complete biliary obstruction. • GI intolerability • Drug-Drug interaction if BAS not separated from other oral medications (other medications 1 or 2 hours before or 4-6 hours after the BAS)
Switch to atorvastatin 80 mg	• Clinically significant LFT elevation occurred more often in the high-dose atorvastatin vs. high-dose simvastatin group in two head to head studies.

ASA=aspirin, LFTs=liver function tests, TG=triglycerides, ULN=upper limit of normal

Niaspan

Weeks	Daily Dose	Administration Schedule
1 to 4	500 mg	1X 500 mg-at bedtime
5 to 8	1000 mg	2X 500 mg-at bedtime
After week 8, titrate to patient response and tolerance. Daily dose of Niaspan should not be increased by more than 500 mg in any 4-week period and daily doses greater than 2000 mg are not recommended.	1500 mg 2000 mg	2X 750 mg-at bedtime or 3X 500 mg-at bedtime 2X 1000 mg-at bedtime or 4X 500 mg-at bedtime

Manufacturer recommends administering Niaspan at bedtime after a low fat snack. Administration on an empty stomach is not recommended.

Crystalline Niacin (Immediate-release) Example titration schedule

Weeks	Daily Dose	Administration Schedule
1	300 mg	100 mg three times daily
2	600 mg	2X 100 mg three times daily
3	900 mg	3X 100 mg three times daily
4	1200 mg	4X 100 mg three times daily
5	1500 mg	1X 500 mg three times daily

Further adjustments as tolerated using 500 or 750 mg tablets up to a maximum of 4.5 g/day

More detailed information regarding ezetimibe and references used can be obtained from the ezetimibe monograph located on the following websites: http://www.pbm.va.gov or http://vaww.pbm.va.gov. Updated versions may be found on the same websites.